

# Occupational Pesticide Use and Risk of Renal Cell Carcinoma in the Agricultural Health Study

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**BACKGROUND:** Agricultural work and occupational pesticide use have been associated with increased risk of renal cell carcinoma (RCC), the most common form of kidney cancer. However, few prospective studies have investigated links to specific pesticides.

**OBJECTIVE:** We evaluated the lifetime use of individual pesticides and the incidence of RCC.

**METHODS:** We evaluated the associations between intensity-weighted lifetime days (IWDs) of 38 pesticides and incident RCC in the Agricultural Health Study, a prospective cohort of licensed pesticide applicators in Iowa and North Carolina. Among 55,873 applicators, 308 cases were diagnosed between enrollment (1993–1997) and the end of follow-up (2014–2015). We estimated incidence rate ratios (RRs) and 95% confidence intervals (CIs) using Poisson regression, controlling for potential confounding factors, with lagged and unlagged pesticide exposures.

**RESULTS:** There was a statistically significant increased risk of RCC among the highest users of 2,4,5-T compared with never users [unlagged  $RR_{IWD\text{ Tertile }3} = 2.92$  (95% CI: 1.65, 5.17;  $p_{trend} = 0.001$ )], with similar risk estimates for lagged exposure [20-y lag  $RR_{IWD\text{ Tertile }3} = 3.37$  (95% CI: 1.83, 6.22;  $p_{trend} = 0.001$ )]. In 20-y lagged analyses, we also found exposure–response associations with chlorpyrifos [ $RR_{IWD\text{ Quartile }4} = 1.68$  (95% CI: 1.05, 2.70;  $p_{trend} = 0.01$ )], chlordane [ $RR_{IWD\text{ Tertile }3} = 2.06$  (95% CI: 1.10, 3.87;  $p_{trend} = 0.02$ )], atrazine [ $RR_{IWD\text{ Quartile }4} = 1.43$  (95% CI: 1.00, 2.03;  $p_{trend} = 0.02$ )], cyanazine [ $RR_{IWD\text{ Quartile }4} = 1.61$  (95% CI: 1.03, 2.50;  $p_{trend} = 0.02$ )], and paraquat [ $RR_{IWD > Median} = 1.95$  (95% CI: 1.03, 3.70;  $p_{trend} = 0.04$ )].

**CONCLUSIONS:** This is, to our knowledge, the first prospective study to evaluate RCC risk in relation to various pesticides. We found evidence of associations with RCC for four herbicides (2,4,5-T, atrazine, cyanazine, and paraquat) and two insecticides (chlorpyrifos and chlordane). Our findings provide insights into specific chemicals that may influence RCC risk among pesticide applicators. Confirmation of these findings and investigations of the biologic plausibility and potential mechanisms underlying the observed associations are warranted. <https://doi.org/10.1289/EHP6334>

## Introduction

The incidence of renal cell carcinoma (RCC), the most common form of kidney cancer, has been steadily increasing in the United States for several decades (Noone et al. 2018; Chow et al. 2018). In addition to male sex, older age, black or African American race, and family history/genetic susceptibility, established risk factors include obesity, hypertension, and cigarette smoking (Chow et al. 2018). Several case–control studies suggest an association of RCC with agricultural work (Parent et al. 2000; Buzio et al. 2002; Zhang et al. 2004; Heck et al. 2010; Karami et al. 2012) as well as with occupational pesticide exposure (Mellemegaard et al. 1994; Hu et al. 2002; Buzio et al. 2002; Karami et al. 2008). Prospective cohort studies of specific pesticides and RCC are limited (Xie et al. 2016). In the Agricultural Health Study (AHS), a large prospective U.S.-based cohort of licensed pesticide applicators, investigations of trifluralin (63 cases) (Kang et al. 2008) and diazinon (94 cases) (Jones et al. 2015) showed nonsignificant increased risks of kidney cancer among the highest users of each pesticide compared with

nonusers. In the present analysis, we used AHS data to evaluate the incidence of RCC in relation to 38 individual pesticides with over 20 y of follow-up. This is, to our knowledge, the first prospective study to comprehensively evaluate RCC risk in relation to lifetime use of individual pesticides.

## Methods

### Study Design

The AHS enrolled 57,310 individuals seeking licenses to apply restricted-use pesticides in Iowa and North Carolina between 1993 and 1997 (Alavanja et al. 1996). All participants completed a self-administered questionnaire at enrollment, and 44% completed an additional take-home questionnaire soliciting more detailed information about the use of some pesticides. A follow-up telephone interview was also completed by 63% of the participants between 1999 and 2005. Participants indicated informed consent by completing the enrollment questionnaire. The study questionnaires are available on the AHS website (<https://aghealth.nih.gov/collaboration/questionnaires.html>).

Lifetime use of 50 selected pesticides was ascertained by self-report in the enrollment and take-home questionnaires and the follow-up interview. At enrollment, participants reported ever/never use of 50 pesticides and more detailed information for 22 of the pesticides (i.e., years and days per year each pesticide was applied, use of personal protective equipment, and pesticide application method). For the remaining 28 pesticides, more detailed information about their use was ascertained on the take-home questionnaire. The midpoints of the categories were multiplied to obtain an estimate of cumulative days of exposure at enrollment. In the 1999–2005 interview, applicators reported the number of days each pesticide was used in the most recent year farmed. If the last year the applicator farmed was after study enrollment, we assumed pesticide application for the number of

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days per year reported at follow-up interview for each year from enrollment through the last year farmed. For each pesticide, we created two metrics of lifetime exposure: lifetime days (days per year  $\times$  number of years), and intensity-weighted lifetime days (lifetime days  $\times$  intensity score). The intensity score was a literature-based algorithm including applicator-provided, exposure-modifying factors from two exposure monitoring studies within the cohort (Coble et al. 2011). Enrollment and follow-up exposure information were combined to generate estimates of cumulative lifetime days and intensity-weighted lifetime days of use.

For participants who did not complete the 1999–2005 interview (37%), we applied a data-driven multiple imputation procedure (five imputations) to impute pesticide use after enrollment using information on demographics, medical history, farm characteristics, and pesticide use from participants who completed both the enrollment and follow-up questionnaires. Ever use and days per year of specific pesticides were imputed for participants who did not complete the follow-up questionnaire and were combined with enrollment data to generate cumulative exposure metrics (Heltshie et al. 2012).

Linkage to state cancer registries provided information on incident cancers diagnosed between enrollment and end of follow-up (2015 in Iowa, 2014 in North Carolina). Cancer diagnoses were classified according to the *International Classification of Disease–Oncology, Third Revision* (ICD-O-3) (Fritz et al. 2000). RCC was defined as ICD-O-3 code C64.9 and all cases were histologically confirmed. Vital status was ascertained via state mortality registries and the National Death Index. For this analysis, individuals accrued person-time from enrollment until the earliest of the following events: moved out of state, any cancer diagnosis, death, or end of follow-up. Participants were followed for incident RCC diagnoses for an average of 19.5 y. After excluding individuals with a history of cancer at enrollment ( $n = 1,096$ ) or those who did not live in either Iowa or North Carolina ( $n = 341$ ), this analysis included 55,873 applicators, with 308 RCC cases diagnosed during follow-up. The study was approved by the institutional review boards of the National Cancer Institute and the other participating institutions.

### Statistical Analysis

We evaluated 38 of the 50 pesticides with at least 20 exposed cases. Based on the distribution among the RCC cases, we categorized both metrics of exposure for each pesticide into quartiles, tertiles, or the median such that there were at least 10 exposed cases in each category. All analyses were conducted with AHS data releases P1REL201701 and P2REL201701. Using SAS (version 9.3; SAS Institute, Inc.), we conducted Poisson regression to calculate incidence rate ratios (RRs) and 95% confidence intervals (CIs) and used PROC MIANALYZE to obtain variance estimates that accounted for the multiple imputations. We used the Wald test to evaluate linear trends with the median of each exposure category as a continuous variable. All models were adjusted for state (Iowa, North Carolina) and factors known to be associated with RCC, including attained age (age at end of follow-up), cigarette smoking status (never, former, current, missing), and body mass index (BMI;  $<25$ ,  $25$ – $30$ ,  $>30$  kg/m<sup>2</sup>, missing). We also adjusted for ever use of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) given that this herbicide was significantly associated with RCC in this analysis, and there was strong *a priori* evidence of an association with RCC. RR and linear trend associations with a  $p < 0.05$  were considered statistically significant. Missing values were retained by modeling as a separate category so that participants with missing values were not dropped. In addition to analyses of overall cumulative use of each pesticide, we also conducted analyses with

10- and 20-y lagged exposures. For these lagged analyses, we estimated cumulative exposure for each year of follow-up until cancer diagnosis, death, movement out of state, or end of follow-up, and then discounted exposure during the years most proximal to cancer diagnosis or other censoring event. We also examined RR patterns for continuous 20-y lagged intensity-weighted lifetime days for selected chemicals ( $d$ ) using one ( $\beta$ ) and two ( $\beta$ ,  $\gamma$ ) parameter models. Specifically, we fitted the following forms:  $RR(d) = \exp(\beta d + \gamma d^2)$ ,  $RR(d) = \exp[\beta \ln(d) + \gamma \{\ln(d)\}^2]$ , and  $RR(d) = \exp\{\beta d + \gamma \ln(d)\}$ , and for the excess RR we fitted the linear-exponential form,  $RR(d) = 1 + \beta d e^{\gamma d}$ . For the model with the smallest Akaike information criterion, we compared the continuous modeling with the category-specific RRs and tested the hypothesis of a null association using a chi-square distribution with 1 ( $\beta = 0$ ) or 2 degrees of freedom ( $\beta = 0$ ,  $\gamma = 0$ ).

In sensitivity analyses, we assessed potential confounding from other factors such as pack-years of cigarette smoking, alcohol consumption, history of hypertension, and family history of cancer, as well as the most highly correlated pesticides based on Spearman correlation coefficients for intensity-weighted lifetime days of use. We also evaluated RCC risk using unlagged intensity-weighted days of pesticide use for participants who completed or did not complete the follow-up questionnaire, as well restricting the analysis to pesticide use reported at enrollment.

### Results

Participants who developed RCC tended to be older, to have a higher BMI, and more likely to have a history of smoking at enrollment compared with those who did not develop RCC (Table 1). Table 2 shows the rate ratios for RCC in relation to unlagged and 10- and 20-y lagged intensity-weighted lifetime days of use of 38 individual pesticides, including herbicides, insecticides, fungicides, and one fumigant. We found statistically significant increased risks of RCC among the highest users of 2,4,5-T compared with never users of this herbicide in the unlagged [ $RR_{T3} = 2.92$  (95% CI: 1.65, 5.17;  $p_{trend} = 0.001$ )], as well as lagged analyses [10-y:  $RR_{T3} = 2.94$  (95% CI: 1.63, 5.31;  $p_{trend} = 0.002$ ); 20-y:  $RR_{T3} = 3.37$  (95% CI: 1.83, 6.22;  $p_{trend} = 0.001$ )] (Table 2). Given the strong and consistent association for 2,4,5-T, we adjusted for use of this herbicide in all analyses of other pesticides. Increased risks of RCC were also seen for high users of cyanazine compared with never users of this herbicide in the lagged analyses [10-y:  $RR_{Q4} = 1.59$  (95% CI: 1.05, 2.39;  $p_{trend} = 0.01$ ); 20-y:  $RR_{Q4} = 1.61$  (95% CI: 1.03, 2.50;  $p_{trend} = 0.02$ )]. We also observed increased risks of RCC among the highest users of chlorpyrifos compared with never users of this insecticide in lagged analyses [10-y:  $RR_{Q4} = 1.51$  (95% CI: 1.02, 2.22;  $p_{trend} = 0.03$ ); 20-y:  $RR_{Q4} = 1.68$  (95% CI: 1.05, 2.70;  $p_{trend} = 0.01$ )]. In the 20-y lagged analyses, we also observed increased risks of RCC among those in the highest categories of atrazine [ $RR_{Q3} = 1.50$  (95% CI: 1.05, 2.14);  $RR_{Q4} = 1.43$  (95% CI: 1.00, 2.03;  $p_{trend} = 0.02$ )], chlordane [ $RR_{T3} = 2.06$  (95% CI: 1.10, 3.87;  $p_{trend} = 0.02$ )], and paraquat [ $RR_{M2} = 1.95$  (95% CI: 1.03, 3.70;  $p_{trend} = 0.04$ )] compared with never users of each pesticide.

Using a continuous model to evaluate the 20-y lagged intensity-weighted lifetime days of 2,4,5-T, atrazine, cyanazine, paraquat, chlordane, and chlorpyrifos and RCC, we found that the risks aligned well with the categorical pesticide use results (see Figure S1). The associations for these pesticides remained essentially unchanged when we further adjusted for pack-years of cigarette smoking, alcohol consumption, history of hypertension, and family history of any cancer, as well as ever use of the most highly correlated pesticides (Spearman correlations of intensity-weighted lifetime days) {cyanazine [ $\rho(r) = 0.6$ ] and alachlor ( $r = 0.6$ ) for atrazine; metolachlor ( $r = 0.6$ ), *S*-ethyl dipropyl dipropylthiocarbamate (EPTC) ( $r = 0.6$ ), and atrazine ( $r = 0.6$ ) for cyanazine; butylate

**Table 1.** Selected characteristics of the Agricultural Health Study population with and without renal cell carcinoma (RCC).

| Characteristics                                | Participants with RCC |       | Participants without RCC |       |
|--|-----------------------|-------|--------------------------|-------|
|  | <i>n</i>              | %     | <i>n</i>                 | %     |
| Total  | 308                   | 100.0 | 55,565                   | 100.0 |
| Gender   |                       |       |                          |       |
| Male   | 303                   | 98.4  | 54,039                   | 97.3  |
| Female   | 5                     | 1.6   | 1,526                    | 2.7   |
| Age at enrollment                              |                       |       |                          |       |
| <40  | 41                    | 13.3  | 17,999                   | 32.4  |
| 40–49  | 66                    | 21.4  | 15,329                   | 27.6  |
| 50–59  | 99                    | 32.1  | 11,452                   | 20.6  |
| 60–69  | 77                    | 25.0  | 7,950                    | 14.3  |
| ≥70  | 25                    | 8.1   | 2,835                    | 5.1   |
| Race   |                       |       |                          |       |
| White  | 299                   | 97.1  | 52,998                   | 95.4  |
| Black and other                                | 9                     | 2.9   | 1,501                    | 2.7   |
| Missing  | 0                     | 0.0   | 1,066                    | 1.9   |
| State at recruitment                           |                       |       |                          |       |
| Iowa   | 183                   | 59.4  | 35,558                   | 64.0  |
| North Carolina                                 | 125                   | 40.6  | 20,007                   | 36.0  |
| Applicator type                                |                       |       |                          |       |
| Private  | 296                   | 96.1  | 50,869                   | 91.5  |
| Commercial                                     | 12                    | 3.9   | 4,696                    | 8.5   |
| Highest education                              |                       |       |                          |       |
| High school or less                            | 184                   | 59.7  | 30,441                   | 54.8  |
| Beyond high school                             | 110                   | 35.7  | 22,778                   | 41.0  |
| Missing  | 14                    | 4.5   | 2,346                    | 4.2   |
| Body mass index (kg/m <sup>2</sup> )           |                       |       |                          |       |
| <25  | 42                    | 13.6  | 10,564                   | 19.0  |
| 25–<30   | 93                    | 30.2  | 20,280                   | 36.5  |
| ≥30  | 74                    | 24.0  | 9,356                    | 16.8  |
| Missing  | 99                    | 32.1  | 15,365                   | 27.7  |
| Cigarette smoking status                       |                       |       |                          |       |
| Never  | 142                   | 46.1  | 28,443                   | 51.2  |
| Former   | 111                   | 36.0  | 16,074                   | 28.9  |
| Current  | 46                    | 14.9  | 9,136                    | 16.4  |
| Missing  | 9                     | 2.9   | 1,912                    | 3.4   |
| Cigarette smoking (pack-years)                 |                       |       |                          |       |
| Never  | 142                   | 46.1  | 28,443                   | 51.2  |
| Former   |                       |       |                          |       |
| Tertile 1                                      | 31                    | 10.1  | 5,396                    | 9.7   |
| Tertile 2                                      | 33                    | 10.7  | 4,892                    | 8.8   |
| Tertile 3                                      | 40                    | 13.0  | 4,653                    | 8.4   |
| Current  |                       |       |                          |       |
| Tertile 1                                      | 14                    | 4.5   | 3,123                    | 5.6   |
| Tertile 2                                      | 6                     | 1.9   | 2,864                    | 5.2   |
| Tertile 3                                      | 22                    | 7.1   | 2,948                    | 5.3   |
| Missing  | 20                    | 6.5   | 3,246                    | 5.8   |
| Ever drink alcohol in year prior to enrollment |                       |       |                          |       |
| Never  | 109                   | 35.4  | 16,819                   | 30.3  |
| Ever   | 179                   | 58.1  | 35,176                   | 63.3  |
| Missing  | 20                    | 6.5   | 3,570                    | 6.4   |
| History of hypertension                        |                       |       |                          |       |
| No   | 91                    | 29.5  | 20,106                   | 36.2  |
| Yes  | 43                    | 14.0  | 3,884                    | 7.0   |
| Missing  | 174                   | 56.5  | 31,575                   | 56.8  |
| Family history of cancer                       |                       |       |                          |       |
| No   | 127                   | 41.2  | 30,504                   | 54.9  |
| Yes  | 155                   | 50.3  | 20,922                   | 37.7  |
| Missing  | 26                    | 8.4   | 4,139                    | 7.4   |

Note: Data from the enrollment questionnaire.

for paraquat ( $r=0.4$ ); 2-(2,4,5-trichlorophenoxy) propionic acid (2,4,5-TP) for 2,4,5-T ( $r=0.6$ ); fonofos ( $r=0.4$ ); and carbofuran ( $r=0.4$ ) for chlorpyrifos; dieldrin for chlordane ( $r=0.6$ ) (see Table S1). Spearman correlation coefficients for the main pesticides of

interest are shown in Table S2. Using the unlagged intensity-weighted lifetime days of pesticide use, we noted similar patterns of associations for participants who completed ( $n$  total = 35,487,  $n$  RCC cases = 177) or did not complete the follow-up questionnaire ( $n$  total = 20,386,  $n$  RCC cases = 133) (see Table S3). Furthermore, similar results were seen when we restricted the analysis to pesticide use reported only at enrollment ( $n$  total = 55,873,  $n$  RCC cases = 308) (see Table S3).

We also found suggestive, but nonstatistically significant exposure–response associations with several other herbicides in the 20-y lagged analyses of intensity-weighted lifetime days (Table 2). Risk of RCC was elevated among the highest users of pendimethalin [ $RR_{T3}=1.73$  (95% CI: 0.92, 3.23;  $p_{trend}=0.05$ )], glyphosate [ $RR_{Q4}=1.49$  (95% CI: 1.01, 2.19;  $p_{trend}=0.07$ )], and dicamba [ $RR_{Q4}=1.50$  (95% CI: 0.97, 2.30;  $p_{trend}=0.08$ )] compared with nonusers of each pesticide.

The patterns of association for lifetime days of each pesticide and RCC were generally the same as those for intensity-weighted days, with elevated risks for 2,4,5-T, atrazine, cyanazine, chlorpyrifos, and chlordane (see Table S4). In addition, in the 10-y lagged analysis the association for lifetime days of metalaxyl was statistically significant [ $RR_{M2}=2.10$  (95% CI: 1.14, 3.86;  $p_{trend}=0.02$ )]; and in the 20-y lagged analyses, the association for lifetime days of pendimethalin [ $RR_{T3}=2.08$  (95% CI: 1.11, 3.89;  $p_{trend}=0.02$ )] and dichlorvos [ $RR_{T3}=1.91$  (95% CI: 1.01, 3.61;  $p_{trend}=0.05$ )] were statistically significant among the highest users compared with nonusers.

## Discussion

In this prospective investigation of RCC in the AHS cohort, we observed statistically significant elevated risks of RCC for the herbicide 2,4,5-T in both unlagged and lagged analyses. We also found statistically significant exposure–response associations in lagged analyses of three other herbicides (atrazine, cyanazine, and paraquat) and two insecticides (chlorpyrifos and chlordane). These findings are summarized in Table 3 in the context of available mechanistic and experimental evidence for pathways relevant to renal carcinogenesis along with evidence from prior epidemiologic investigations of kidney cancer and nonmalignant kidney disease.

To our knowledge, this is the first epidemiologic study reporting an association with RCC incidence for 2,4,5-T, a chlorophenoxy acetic acid herbicide used to defoliate broad-leaved plants. This herbicide was developed in the 1940s, phased out in the late 1970s, and banned by the mid-1980s (U.S. EPA 1984; Lilienfeld and Gallo 1989). This is reflected in the frequency of its use in the AHS, with 20% of the cohort reporting a history of 2,4,5-T use at enrollment, and virtually no use between enrollment and the follow-up interview. The International Agency for Research on Cancer (IARC) classified chlorophenoxy herbicides as possibly carcinogenic to humans based mainly on laboratory animal data (IARC 1987). One of the primary health concerns related to 2,4,5-T is its historical contamination during manufacture with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a persistent organic pollutant classified as a known carcinogen (IARC 1997). TCDD, the most toxic form of dioxin, has been linked with several cancers including lung cancer, Hodgkin lymphoma, and soft-tissue sarcoma (Baan et al. 2009). A 1997 cancer mortality study of workers producing phenoxy herbicides or chlorophenols found a statistically significant excess of kidney cancer among workers considered exposed to TCDD or higher chlorinated dioxins (Kogevinas et al. 1997). A 2016 meta-analysis of TCDD exposure found a statistically significant excess mortality for kidney cancer but did not evaluate kidney cancer incidence (Xu et al. 2016). Mechanisms linking TCDD and cancer have not been established; however, aryl hydrocarbon receptor (AhR) activation

**Table 2.** Renal cell carcinoma (RCC) incidence in relation to intensity-weighted lifetime days of pesticide use in the Agricultural Health Study.

| Pesticide use <sup>a</sup>     | Unlagged exposure         |                 |                     |  | 10-y lagged exposure <sup>b</sup> |                 |                     |  | 20-y lagged exposure <sup>b</sup> |                 |                     |  |
|--------------------------------|---------------------------|-----------------|---------------------|--|-----------------------------------|-----------------|---------------------|--|-----------------------------------|-----------------|---------------------|--|
|                                | <i>n</i> RCC <sup>c</sup> | RR <sup>d</sup> | 95% CI <sup>d</sup> | <i>p</i> <sub>trend</sub> <sup>d,e</sup> | <i>n</i> RCC <sup>c</sup>         | RR <sup>d</sup> | 95% CI <sup>d</sup> | <i>p</i> <sub>trend</sub> <sup>d,e</sup> | <i>n</i> RCC <sup>c</sup>         | RR <sup>d</sup> | 95% CI <sup>d</sup> | <i>p</i> <sub>trend</sub> <sup>d,e</sup> |
| <b>Herbicides</b>              |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| Anilides/anilines              |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| Alachlor                       |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 127                       | 1.00            | —                   |  | 129                               | 1.00            | —                   |  | 149                               | 1.00            | —                   |  |
| Q1                             | 34                        | 0.95            | 0.64, 1.41          |  | 34                                | 0.78            | 0.53, 1.15          |  | 29                                | 0.93            | 0.62, 1.39          |  |
| Q2                             | 37                        | 1.09            | 0.75, 1.58          |  | 34                                | 1.45            | 0.99, 2.13          |  | 29                                | 1.32            | 0.88, 1.97          |  |
| Q3                             | 33                        | 1.03            | 0.69, 1.52          |  | 34                                | 1.08            | 0.74, 1.58          |  | 29                                | 1.13            | 0.76, 1.69          |  |
| Q4                             | 38                        | 0.85            | 0.59, 1.22          | 0.37                                     | 34                                | 0.88            | 0.60, 1.29          | 0.59                                     | 29                                | 1.02            | 0.69, 1.53          | 0.84                                     |
| Metolachlor                    |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 141                       | 1.00            | —                   |  | 152                               | 1.00            | —                   |  | 188                               | 1.00            | —                   |  |
| Q1                             | 31                        | 0.97            | 0.63, 1.50          |  | 30                                | 1.00            | 0.65, 1.52          |  | 20                                | 1.10            | 0.69, 1.75          |  |
| Q2                             | 34                        | 1.18            | 0.80, 1.74          |  | 30                                | 1.20            | 0.81, 1.78          |  | 21                                | 1.32            | 0.83, 2.07          |  |
| Q3                             | 34                        | 1.06            | 0.71, 1.57          |  | 30                                | 1.12            | 0.74, 1.70          |  | 21                                | 1.13            | 0.72, 1.79          |  |
| Q4                             | 33                        | 0.99            | 0.67, 1.45          | 0.93                                     | 30                                | 1.06            | 0.72, 1.58          | 0.76                                     | 21                                | 1.32            | 0.84, 2.08          | 0.25                                     |
| Pendimethalin                  |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 80                        | 1.00            | —                   |  | 85                                | 1.00            | —                   |  | 100                               | 1.00            | —                   |  |
| T1                             | 21                        | 0.79            | 0.43, 1.44          |  | 18                                | 0.86            | 0.44, 1.67          |  | 9                                 | 0.97            | 0.49, 1.91          |  |
| T2                             | 22                        | 1.26            | 0.78, 2.03          |  | 18                                | 1.23            | 0.74, 2.03          |  | 10                                | 1.84            | 0.96, 3.53          |  |
| T3                             | 23                        | 1.35            | 0.83, 2.22          | 0.15                                     | 19                                | 1.46            | 0.88, 2.40          | 0.11                                     | 11                                | 1.73            | 0.92, 3.23          | 0.05                                     |
| Trifluralin                    |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 125                       | 1.00            | —                   |  | 129                               | 1.00            | —                   |  | 148                               | 1.00            | —                   |  |
| Q1                             | 33                        | 0.83            | 0.55, 1.24          |  | 34                                | 0.89            | 0.60, 1.30          |  | 29                                | 0.89            | 0.59, 1.33          |  |
| Q2                             | 35                        | 1.02            | 0.69, 1.49          |  | 34                                | 1.03            | 0.69, 1.52          |  | 29                                | 1.25            | 0.83, 1.88          |  |
| Q3                             | 36                        | 1.08            | 0.73, 1.60          |  | 34                                | 1.41            | 0.95, 2.08          |  | 29                                | 1.51            | 1.00, 2.27          |  |
| Q4                             | 35                        | 1.16            | 0.79, 1.70          | 0.31                                     | 34                                | 1.06            | 0.72, 1.56          | 0.45                                     | 30                                | 1.10            | 0.73, 1.64          | 0.42                                     |
| Phenoxy                        |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| 2,4-D                          |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 65                        | 1.00            | —                   |  | 75                                | 1.00            | —                   |  | 99                                | 1.00            | —                   |  |
| Q1                             | 58                        | 1.09            | 0.75, 1.57          |  | 54                                | 0.88            | 0.62, 1.26          |  | 47                                | 0.82            | 0.57, 1.16          |  |
| Q2                             | 57                        | 0.80            | 0.55, 1.16          |  | 55                                | 0.95            | 0.66, 1.37          |  | 48                                | 1.22            | 0.85, 1.75          |  |
| Q3                             | 57                        | 1.12            | 0.76, 1.64          |  | 54                                | 1.09            | 0.75, 1.58          |  | 48                                | 1.32            | 0.92, 1.90          |  |
| Q4                             | 57                        | 0.89            | 0.61, 1.31          | 0.66                                     | 55                                | 0.97            | 0.67, 1.41          | 0.82                                     | 48                                | 1.15            | 0.80, 1.66          | 0.23                                     |
| 2,4,5-T                        |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 86                        | 1.00            | —                   |  | 88                                | 1.00            | —                   |  | 90                                | 1.00            | —                   |  |
| T1                             | 11                        | 1.30            | 0.69, 2.45          |  | 11                                | 1.29            | 0.68, 2.43          |  | 11                                | 1.23            | 0.65, 2.31          |  |
| T2                             | 14                        | 1.18            | 0.67, 2.09          |  | 13                                | 1.07            | 0.60, 1.94          |  | 12                                | 1.17            | 0.63, 2.15          |  |
| T3                             | 14                        | 2.92            | 1.65, 5.17          | 0.001                                    | 13                                | 2.94            | 1.63, 5.31          | 0.002                                    | 12                                | 3.37            | 1.83, 6.22          | 0.001                                    |
| Thiocarbamate                  |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| Butylate                       |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 91                        | 1.00            | —                   |  | 91                                | 1.00            | —                   |  | 96                                | 1.00            | —                   |  |
| T1                             | 12                        | 0.89            | 0.48, 1.64          |  | 11                                | 0.94            | 0.50, 1.78          |  | 9                                 | 1.19            | 0.59, 2.37          |  |
| T2                             | 11                        | 0.88            | 0.47, 1.66          |  | 12                                | 0.90            | 0.49, 1.65          |  | 10                                | 0.74            | 0.38, 1.43          |  |
| T3                             | 12                        | 1.64            | 0.89, 3.02          | 0.16                                     | 12                                | 1.75            | 0.95, 3.23          | 0.11                                     | 11                                | 2.16            | 1.15, 4.06          | 0.13                                     |
| EPTC                           |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 214                       | 1.00            | —                   |  | 217                               | 1.00            | —                   |  | 231                               | 1.00            | —                   |  |
| T1                             | 17                        | 1.04            | 0.63, 1.71          |  | 16                                | 1.05            | 0.63, 1.75          |  | 12                                | 0.89            | 0.49, 1.59          |  |
| T2                             | 18                        | 1.05            | 0.64, 1.71          |  | 17                                | 1.10            | 0.67, 1.81          |  | 12                                | 1.49            | 0.83, 2.67          |  |
| T3                             | 19                        | 1.21            | 0.75, 1.95          | 0.44                                     | 18                                | 1.22            | 0.75, 1.98          | 0.42                                     | 13                                | 1.41            | 0.80, 2.48          | 0.17                                     |
| Triazine/triazinone            |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| Atrazine                       |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 81                        | 1.00            | —                   |  | 88                                | 1.00            | —                   |  | 115                               | 1.00            | —                   |  |
| Q1                             | 53                        | 0.98            | 0.68, 1.40          |  | 52                                | 0.98            | 0.68, 1.41          |  | 45                                | 0.86            | 0.60, 1.22          |  |
| Q2                             | 54                        | 1.03            | 0.72, 1.47          |  | 52                                | 1.07            | 0.76, 1.53          |  | 45                                | 1.27            | 0.89, 1.81          |  |
| Q3                             | 53                        | 1.20            | 0.84, 1.72          |  | 51                                | 1.24            | 0.87, 1.78          |  | 45                                | 1.50            | 1.05, 2.14          |  |
| Q4                             | 54                        | 1.11            | 0.78, 1.60          | 0.49                                     | 53                                | 1.21            | 0.85, 1.73          | 0.23                                     | 46                                | 1.43            | 1.00, 2.03          | 0.02                                     |
| Cyanazine                      |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 151                       | 1.00            | —                   |  | 153                               | 1.00            | —                   |  | 170                               | 1.00            | —                   |  |
| Q1                             | 28                        | 1.07            | 0.71, 1.64          |  | 28                                | 0.95            | 0.63, 1.45          |  | 24                                | 1.22            | 0.78, 1.89          |  |
| Q2                             | 29                        | 0.92            | 0.60, 1.39          |  | 28                                | 1.15            | 0.75, 1.74          |  | 24                                | 1.21            | 0.77, 1.88          |  |
| Q3                             | 29                        | 1.44            | 0.95, 2.19          |  | 27                                | 1.48            | 0.96, 2.27          |  | 24                                | 1.86            | 1.19, 2.90          |  |
| Q4                             | 29                        | 1.40            | 0.92, 2.12          | 0.07                                     | 30                                | 1.59            | 1.05, 2.39          | 0.01                                     | 24                                | 1.61            | 1.03, 2.50          | 0.02                                     |
| Metribuzin                     |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 83                        | 1.00            | —                   |  | 85                                | 1.00            | —                   |  | 94                                | 1.00            | —                   |  |
| T1                             | 15                        | 0.82            | 0.54, 1.25          |  | 14                                | 0.99            | 0.55, 1.76          |  | 11                                | 1.00            | 0.53, 1.90          |  |
| T2                             | 16                        | 0.82            | 0.57, 1.18          |  | 15                                | 0.73            | 0.41, 1.31          |  | 11                                | 0.82            | 0.44, 1.56          |  |
| T3                             | 16                        | 1.03            | 0.67, 1.59          | 0.99                                     | 16                                | 1.10            | 0.63, 1.90          | 0.90                                     | 12                                | 1.28            | 0.69, 2.36          | 0.54                                     |
| Other                          |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| Chlorimuron ethyl <sup>f</sup> |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                           | 92                        | 1.00            | —                   |  | 95                                | 1.00            | —                   |  | 113                               | 1.00            | —                   |  |
| T1                             | 14                        | 0.89            | 0.50, 1.60          |  | 12                                | 1.17            | 0.63, 2.19          |  | 7                                 | 0.96            | 0.45, 2.07          |  |
| T2                             | 14                        | 0.91            | 0.51, 1.61          |  | 12                                | 0.88            | 0.47, 1.65          |  | 8                                 | 1.17            | 0.57, 2.41          | 0.67                                     |
| T3                             | 15                        | 1.20            | 0.68, 2.11          | 0.55                                     | 13                                | 1.35            | 0.75, 2.45          | 0.39                                     | —                                 | —               | —                   |  |

Table 2. (Continued.)

| Pesticide use <sup>a</sup> | Unlagged exposure         |                 |                     |  | 10-y lagged exposure <sup>b</sup> |                 |                     |  | 20-y lagged exposure <sup>b</sup> |                 |                     |  |
|----------------------------|---------------------------|-----------------|---------------------|--|-----------------------------------|-----------------|---------------------|--|-----------------------------------|-----------------|---------------------|--|
|                            | <i>n</i> RCC <sup>c</sup> | RR <sup>d</sup> | 95% CI <sup>d</sup> | <i>p</i> <sub>trend</sub> <sup>d,e</sup> | <i>n</i> RCC <sup>c</sup>         | RR <sup>d</sup> | 95% CI <sup>d</sup> | <i>p</i> <sub>trend</sub> <sup>d,e</sup> | <i>n</i> RCC <sup>c</sup>         | RR <sup>d</sup> | 95% CI <sup>d</sup> | <i>p</i> <sub>trend</sub> <sup>d,e</sup> |
| Dicamba                    |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 126                       | 1.00            | —                   |  | 135                               | 1.00            | —                   |  | 157                               | 1.00            | —                   |  |
| Q1                         | 33                        | 0.91            | 0.60, 1.37          |  | 31                                | 0.88            | 0.58, 1.33          |  | 26                                | 1.09            | 0.71, 1.68          |  |
| Q2                         | 33                        | 0.90            | 0.58, 1.39          |  | 31                                | 0.99            | 0.64, 1.54          |  | 25                                | 1.72            | 1.11, 2.68          |  |
| Q3                         | 34                        | 1.09            | 0.71, 1.66          |  | 30                                | 1.03            | 0.67, 1.59          |  | 26                                | 1.20            | 0.78, 1.85          |  |
| Q4                         | 33                        | 1.07            | 0.70, 1.62          | 0.56                                     | 32                                | 1.21            | 0.80, 1.82          | 0.27                                     | 26                                | 1.50            | 0.97, 2.30          | 0.08                                     |
| Glyphosate                 |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 54                        | 1.00            | —                   |  | 75                                | 1.00            | —                   |  | 164                               | 1.00            | —                   |  |
| Q1                         | 59                        | 1.00            | 0.68, 1.47          |  | 54                                | 1.09            | 0.76, 1.57          |  | 31                                | 1.09            | 0.74, 1.60          |  |
| Q2                         | 59                        | 0.94            | 0.64, 1.39          |  | 54                                | 1.15            | 0.80, 1.64          |  | 32                                | 1.26            | 0.86, 1.85          |  |
| Q3                         | 58                        | 1.06            | 0.73, 1.56          |  | 54                                | 1.25            | 0.83, 1.87          |  | 32                                | 0.90            | 0.61, 1.32          |  |
| Q4                         | 61                        | 1.06            | 0.72, 1.57          | 0.65                                     | 55                                | 1.39            | 0.97, 1.99          | 0.08                                     | 32                                | 1.49            | 1.01, 2.19          | 0.07                                     |
| Imazethapyr                |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 173                       | 1.00            | —                   |  | 189                               | 1.00            | —                   |  | 230                               | 1.00            | —                   |  |
| T1                         | 31                        | 0.65            | 0.43, 0.97          |  | 25                                | 0.77            | 0.50, 1.18          |  | 12                                | 1.03            | 0.57, 1.85          |  |
| T2                         | 31                        | 0.80            | 0.53, 1.21          |  | 26                                | 0.93            | 0.59, 1.46          |  | 12                                | 1.28            | 0.71, 2.30          |  |
| T3                         | 32                        | 0.75            | 0.50, 1.13          | 0.28                                     | 27                                | 0.91            | 0.60, 1.38          | 0.75                                     | 13                                | 1.36            | 0.78, 2.40          | 0.22                                     |
| Paraquat <sup>f</sup>      |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 99                        | 1.00            | —                   |  | 102                               | 1.00            | —                   |  | 106                               | 1.00            | —                   |  |
| T1                         | 11                        | 1.26            | 0.60, 2.66          |  | 11                                | 1.32            | 0.66, 2.67          |  | 12                                | 1.73            | 0.94, 3.18          |  |
| T2                         | 14                        | 2.25            | 1.24, 4.10          |  | 11                                | 2.02            | 1.06, 3.85          |  | 12                                | 1.95            | 1.03, 3.70          | 0.04                                     |
| T3                         | 14                        | 1.51            | 0.78, 2.90          | 0.17                                     | 12                                | 1.42            | 0.70, 2.88          | 0.20                                     | —                                 | —               | —                   |  |
| Petroleum <sup>f</sup>     |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 100                       | 1.00            | —                   |  | 100                               | 1.00            | —                   |  | 110                               | 1.00            | —                   |  |
| T1                         | 9                         | 0.97            | 0.49, 1.94          |  | 9                                 | 1.05            | 0.53, 2.08          |  | 10                                | 1.07            | 0.56, 2.06          |  |
| T2                         | 10                        | 0.86            | 0.45, 1.65          |  | 10                                | 1.12            | 0.58, 2.15          |  | 10                                | 0.99            | 0.51, 1.89          | 0.95                                     |
| T3                         | 10                        | 1.58            | 0.82, 3.05          | 0.19                                     | 10                                | 1.39            | 0.72, 2.68          | 0.32                                     | —                                 | —               | —                   |  |
| Insecticides               |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| Organochlorines            |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| Aldrin                     |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 95                        | 1.00            | —                   |  | 95                                | 1.00            | —                   |  | 95                                | 1.00            | —                   |  |
| T1                         | 10                        | 1.25            | 0.64, 2.46          |  | 10                                | 1.26            | 0.64, 2.48          |  | 10                                | 1.29            | 0.66, 2.53          |  |
| T2                         | 11                        | 0.95            | 0.49, 1.81          |  | 11                                | 0.95            | 0.50, 1.83          |  | 11                                | 0.96            | 0.50, 1.84          |  |
| T3                         | 11                        | 1.46            | 0.76, 2.81          | 0.29                                     | 11                                | 1.48            | 0.77, 2.84          | 0.28                                     | 11                                | 1.68            | 0.87, 3.24          | 0.14                                     |
| Chlordane                  |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 95                        | 1.00            | —                   |  | 96                                | 1.00            | —                   |  | 97                                | 1.00            | —                   |  |
| T1                         | 11                        | 1.01            | 0.53, 1.90          |  | 11                                | 1.01            | 0.53, 1.90          |  | 10                                | 1.05            | 0.54, 2.04          |  |
| T2                         | 12                        | 1.01            | 0.54, 1.86          |  | 11                                | 0.94            | 0.50, 1.78          |  | 11                                | 0.97            | 0.51, 1.83          |  |
| T3                         | 12                        | 1.72            | 0.92, 3.23          | 0.09                                     | 12                                | 1.72            | 0.92, 3.23          | 0.08                                     | 12                                | 2.06            | 1.10, 3.87          | 0.02                                     |
| DDT                        |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 86                        | 1.00            | —                   |  | 86                                | 1.00            | —                   |  | 88                                | 1.00            | —                   |  |
| T1                         | 15                        | 1.25            | 0.70, 2.22          |  | 15                                | 1.25            | 0.70, 2.23          |  | 12                                | 0.91            | 0.48, 1.70          |  |
| T2                         | 14                        | 0.76            | 0.42, 1.38          |  | 14                                | 0.77            | 0.42, 1.39          |  | 15                                | 0.87            | 0.49, 1.54          |  |
| T3                         | 15                        | 1.39            | 0.78, 2.51          | 0.29                                     | 15                                | 1.41            | 0.78, 2.53          | 0.28                                     | 15                                | 1.41            | 0.78, 2.53          | 0.20                                     |
| Heptachlor                 |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 106                       | 1.00            | —                   |  | 106                               | 1.00            | —                   |  | 108                               | 1.00            | —                   |  |
| M1                         | 11                        | 0.98            | 0.52, 1.87          |  | 11                                | 0.99            | 0.52, 1.89          |  | 9                                 | 0.80            | 0.39, 1.61          |  |
| M2                         | 12                        | 1.32            | 0.71, 2.46          | 0.40                                     | 12                                | 1.34            | 0.72, 2.49          | 0.38                                     | 12                                | 1.44            | 0.77, 2.69          | 0.34                                     |
| Lindane                    |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 109                       | 1.00            | —                   |  | 109                               | 1.00            | —                   |  | 113                               | 1.00            | —                   |  |
| M1                         | 10                        | 0.76            | 0.39, 1.46          |  | 10                                | 1.04            | 0.54, 1.99          |  | 8                                 | 0.91            | 0.44, 1.89          |  |
| M2                         | 11                        | 1.50            | 0.80, 2.80          | 0.20                                     | 11                                | 1.17            | 0.62, 2.19          | 0.63                                     | 8                                 | 1.00            | 0.48, 2.08          | 0.99                                     |
| Toxaphene                  |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 109                       | 1.00            | —                   |  | 109                               | 1.00            | —                   |  | 110                               | 1.00            | —                   |  |
| M1                         | 11                        | 1.61            | 0.86, 3.02          |  | 11                                | 1.63            | 0.87, 3.05          |  | 10                                | 1.79            | 0.93, 3.45          |  |
| M2                         | 11                        | 1.02            | 0.54, 1.93          | 0.99                                     | 11                                | 1.03            | 0.54, 1.95          | 0.95                                     | 11                                | 0.99            | 0.52, 1.88          | 0.90                                     |
| Organophosphates           |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| Chlorpyrifos               |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 172                       | 1.00            | —                   |  | 176                               | 1.00            | —                   |  | 219                               | 1.00            | —                   |  |
| Q1                         | 30                        | 0.92            | 0.61, 1.37          |  | 29                                | 0.99            | 0.66, 1.47          |  | 19                                | 1.11            | 0.70, 1.78          |  |
| Q2                         | 31                        | 0.89            | 0.61, 1.31          |  | 31                                | 1.17            | 0.79, 1.73          |  | 19                                | 1.13            | 0.70, 1.81          |  |
| Q3                         | 31                        | 1.19            | 0.79, 1.78          |  | 29                                | 1.20            | 0.80, 1.81          |  | 19                                | 1.52            | 0.95, 2.43          |  |
| Q4                         | 31                        | 1.21            | 0.82, 1.78          | 0.23                                     | 30                                | 1.51            | 1.02, 2.22          | 0.03                                     | 19                                | 1.68            | 1.05, 2.70          | 0.01                                     |
| Diazinon <sup>f</sup>      |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                       | 98                        | 1.00            | —                   |  | 102                               | 1.00            | —                   |  | 108                               | 1.00            | —                   |  |
| T1                         | 11                        | 0.96            | 0.44, 2.09          |  | 10                                | 0.99            | 0.48, 2.04          |  | 10                                | 0.80            | 0.42, 1.54          |  |
| T2                         | 12                        | 0.83            | 0.45, 1.54          |  | 10                                | 0.84            | 0.43, 1.62          |  | 11                                | 1.36            | 0.72, 2.58          | 0.34                                     |
| T3                         | 12                        | 1.22            | 0.65, 2.29          | 0.55                                     | 11                                | 1.18            | 0.62, 2.25          | 0.64                                     | —                                 | —               | —                   |  |

Table 2. (Continued.)

| Pesticide use <sup>a</sup>      | Unlagged exposure         |                 |                     |  | 10-y lagged exposure <sup>b</sup> |                 |                     |  | 20-y lagged exposure <sup>b</sup> |                 |                     |  |
|---------------------------------|---------------------------|-----------------|---------------------|--|-----------------------------------|-----------------|---------------------|--|-----------------------------------|-----------------|---------------------|--|
|                                 | <i>n</i> RCC <sup>c</sup> | RR <sup>d</sup> | 95% CI <sup>d</sup> | <i>p</i> <sub>trend</sub> <sup>d,e</sup> | <i>n</i> RCC <sup>c</sup>         | RR <sup>d</sup> | 95% CI <sup>d</sup> | <i>p</i> <sub>trend</sub> <sup>d,e</sup> | <i>n</i> RCC <sup>c</sup>         | RR <sup>d</sup> | 95% CI <sup>d</sup> | <i>p</i> <sub>trend</sub> <sup>d,e</sup> |
| Dichlorvos                      |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 244                       | 1.00            | —                   |  | 245                               | 1.00            | —                   |  | 247                               | 1.00            | —                   |  |
| T1                              | 10                        | 1.09            | 0.56, 2.12          |  | 9                                 | 1.10            | 0.56, 2.15          |  | 10                                | 1.45            | 0.77, 2.74          |  |
| T2                              | 11                        | 1.25            | 0.68, 2.31          |  | 11                                | 1.35            | 0.73, 2.49          |  | 9                                 | 1.50            | 0.76, 2.92          |  |
| T3                              | 10                        | 1.05            | 0.55, 1.98          | 0.90                                     | 10                                | 1.12            | 0.59, 2.12          | 0.74                                     | 9                                 | 1.32            | 0.67, 2.57          | 0.46                                     |
| Fonofos                         |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 223                       | 1.00            | —                   |  | 225                               | 1.00            | —                   |  | 240                               | 1.00            | —                   |  |
| T1                              | 16                        | 1.24            | 0.74, 2.08          |  | 15                                | 1.15            | 0.68, 1.96          |  | 11                                | 1.02            | 0.55, 1.88          |  |
| T2                              | 16                        | 0.74            | 0.44, 1.24          |  | 16                                | 0.80            | 0.48, 1.34          |  | 10                                | 0.65            | 0.35, 1.24          |  |
| T3                              | 17                        | 0.66            | 0.40, 1.10          | 0.09                                     | 16                                | 0.69            | 0.41, 1.16          | 0.14                                     | 11                                | 0.75            | 0.40, 1.37          | 0.20                                     |
| Malathion                       |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 44                        | 1.00            | —                   |  | 50                                | 1.00            | —                   |  | 61                                | 1.00            | —                   |  |
| T1                              | 34                        | 1.08            | 0.69, 1.71          |  | 31                                | 1.06            | 0.67, 1.69          |  | 22                                | 1.19            | 0.73, 1.96          |  |
| T2                              | 35                        | 0.93            | 0.58, 1.48          |  | 30                                | 0.94            | 0.58, 1.53          |  | 22                                | 0.97            | 0.59, 1.59          |  |
| T3                              | 37                        | 1.08            | 0.69, 1.70          | 0.79                                     | 34                                | 1.04            | 0.66, 1.63          | 0.91                                     | 23                                | 1.16            | 0.71, 1.91          | 0.69                                     |
| Phorate                         |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 81                        | 1.00            | —                   |  | 81                                | 1.00            | —                   |  | 86                                | 1.00            | —                   |  |
| T1                              | 15                        | 1.16            | 0.66, 2.06          |  | 15                                | 1.24            | 0.70, 2.20          |  | 14                                | 1.20            | 0.65, 2.19          |  |
| T2                              | 16                        | 1.66            | 0.95, 2.89          |  | 16                                | 1.72            | 0.99, 3.01          |  | 15                                | 1.99            | 1.12, 3.52          |  |
| T3                              | 17                        | 1.29            | 0.76, 2.21          | 0.38                                     | 17                                | 1.39            | 0.82, 2.38          | 0.27                                     | 14                                | 1.48            | 0.83, 2.63          | 0.23                                     |
| Terbufos                        |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 170                       | 1.00            | —                   |  | 178                               | 1.00            | —                   |  | 208                               | 1.00            | —                   |  |
| T1                              | 32                        | 0.83            | 0.56, 1.23          |  | 30                                | 0.86            | 0.58, 1.28          |  | 20                                | 0.82            | 0.51, 1.30          |  |
| T2                              | 32                        | 1.24            | 0.85, 1.83          |  | 29                                | 1.01            | 0.68, 1.50          |  | 19                                | 0.81            | 0.51, 1.31          |  |
| T3                              | 34                        | 0.98            | 0.68, 1.43          | 0.85                                     | 31                                | 1.10            | 0.75, 1.61          | 0.57                                     | 21                                | 1.33            | 0.84, 2.08          | 0.34                                     |
| Other                           |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| Carbaryl                        |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 71                        | 1.00            | —                   |  | 75                                | 1.00            | —                   |  | 81                                | 1.00            | —                   |  |
| T1                              | 22                        | 0.88            | 0.53, 1.44          |  | 20                                | 0.87            | 0.52, 1.48          |  | 16                                | 1.30            | 0.76, 2.24          |  |
| T2                              | 22                        | 0.71            | 0.42, 1.21          |  | 20                                | 0.81            | 0.48, 1.39          |  | 15                                | 1.17            | 0.66, 2.06          |  |
| T3                              | 24                        | 0.88            | 0.50, 1.56          | 0.93                                     | 22                                | 0.96            | 0.55, 1.68          | 0.91                                     | 17                                | 0.83            | 0.46, 1.49          | 0.40                                     |
| Carbofuran                      |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 197                       | 1.00            | —                   |  | 199                               | 1.00            | —                   |  | 215                               | 1.00            | —                   |  |
| T1                              | 25                        | 0.75            | 0.49, 1.14          |  | 23                                | 0.74            | 0.48, 1.15          |  | 19                                | 0.78            | 0.49, 1.25          |  |
| T2                              | 26                        | 1.18            | 0.78, 1.79          |  | 26                                | 1.24            | 0.82, 1.87          |  | 19                                | 1.42            | 0.89, 2.28          |  |
| T3                              | 27                        | 1.05            | 0.70, 1.57          | 0.64                                     | 26                                | 1.14            | 0.75, 1.72          | 0.38                                     | 21                                | 1.11            | 0.70, 1.74          | 0.46                                     |
| Permethrin (crops) <sup>f</sup> |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 229                       | 1.00            | —                   |  | 234                               | 1.00            | —                   |  | 251                               | 1.00            | —                   |  |
| T1                              | 14                        | 0.96            | 0.55, 1.68          |  | 10                                | 0.78            | 0.41, 1.49          |  | 11                                | 1.50            | 0.82, 2.75          |  |
| T2                              | 15                        | 1.75            | 1.01, 3.01          |  | 15                                | 2.13            | 1.25, 3.63          |  | 11                                | 1.42            | 0.78, 2.61          | 0.16                                     |
| T3                              | 15                        | 1.19            | 0.69, 2.04          | 0.33                                     | 14                                | 1.33            | 0.76, 2.34          | 0.18                                     | —                                 | —               | —                   |  |
| Permethrin (animals)            |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 248                       | 1.00            | —                   |  | 251                               | 1.00            | —                   |  | 261                               | 1.00            | —                   |  |
| M1                              | 14                        | 0.86            | 0.49, 1.52          |  | 12                                | 0.77            | 0.42, 1.42          |  | 7                                 | 0.81            | 0.38, 1.72          |  |
| M2                              | 14                        | 0.86            | 0.50, 1.47          | 0.58                                     | 13                                | 0.96            | 0.55, 1.69          | 0.88                                     | 8                                 | 1.11            | 0.55, 2.25          | 0.78                                     |
| Fungicides                      |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| Captan                          |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 244                       | 1.00            | —                   |  | 245                               | 1.00            | —                   |  | 262                               | 1.00            | —                   |  |
| M1                              | 13                        | 0.96            | 0.54, 1.68          |  | 13                                | 1.33            | 0.76, 2.33          |  | 4                                 | 0.57            | 0.21, 1.54          |  |
| M2                              | 14                        | 0.93            | 0.50, 1.72          | 0.83                                     | 13                                | 1.01            | 0.52, 1.98          | 0.99                                     | 5                                 | 1.16            | 0.47, 2.82          | 0.75                                     |
| Chlorothalonil                  |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 266                       | 1.00            | —                   |  | 270                               | 1.00            | —                   |  | 275                               | 1.00            | —                   |  |
| M1                              | 13                        | 0.96            | 0.54, 1.71          |  | 12                                | 1.00            | 0.56, 1.79          |  | 9                                 | 1.45            | 0.74, 2.85          |  |
| M2                              | 15                        | 1.49            | 0.85, 2.61          | 0.17                                     | 12                                | 1.36            | 0.73, 2.53          | 0.36                                     | 10                                | 1.55            | 0.81, 2.97          | 0.15                                     |
| Metalaxyl                       |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 100                       | 1.00            | —                   |  | 101                               | 1.00            | —                   |  | 110                               | 1.00            | —                   |  |
| M1                              | 14                        | 1.09            | 0.61, 1.97          |  | 14                                | 1.27            | 0.71, 2.28          |  | 8                                 | 1.34            | 0.65, 2.79          |  |
| M2                              | 15                        | 1.56            | 0.83, 2.96          | 0.17                                     | 14                                | 1.66            | 0.88, 3.12          | 0.13                                     | 8                                 | 1.55            | 0.72, 3.32          | 0.28                                     |
| Fumigant                        |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| Methyl bromide                  |                           |                 |                     |  |                                   |                 |                     |  |                                   |                 |                     |  |
| None                            | 248                       | 1.00            | —                   |  | 250                               | 1.00            | —                   |  | 255                               | 1.00            | —                   |  |
| T1                              | 16                        | 0.91            | 0.53, 1.54          |  | 15                                | 0.88            | 0.51, 1.52          |  | 14                                | 1.05            | 0.60, 1.84          |  |
| T2                              | 16                        | 0.97            | 0.57, 1.67          |  | 16                                | 0.99            | 0.58, 1.70          |  | 14                                | 1.08            | 0.62, 1.91          |  |
| T3                              | 17                        | 1.26            | 0.74, 2.14          | 0.37                                     | 16                                | 1.27            | 0.74, 2.18          | 0.36                                     | 15                                | 1.28            | 0.74, 2.23          | 0.38                                     |

Note: —, Data not available; CI, confidence interval; DDT, dichlorodiphenyltrichloroethane; EPTC, *S*-ethyl dipropylthiocarbamate; M, median; *n* RCC, number of renal cell carcinoma cases; Q, quartile; RR, rate ratio; T, tertile; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid.

<sup>a</sup>Cut points based on intensity-weighted days among RCC cases for unlagged and lagged exposures.

<sup>b</sup>Lagged years of pesticide use subtracted from date of last follow-up.

<sup>c</sup>Number of cases may not be consistent across pesticides or across lagged periods due to missing exposure.

<sup>d</sup>Adjusted for age, state of enrollment, cigarette smoking status, body mass index, ever use of 2,4,5-T (not self-adjusted).

<sup>e</sup>Wald test of trend using median of each exposure category.

<sup>f</sup>Median cut points for 20-y lagged exposure.

**Table 3.** Summary of the experimental and epidemiologic evidence linking selected pesticides to kidney damage and risk of renal cell carcinoma (RCC).

| Pesticide            | Mechanistic and experimental evidence for pathways related to RCC development  | Epidemiologic evidence of associations with RCC and/or nonmalignant kidney disease  | Observed associations with RCC in this study  |
|----------------------|--|---|---|
| 2,4,5-T <sup>a</sup> | <ul style="list-style-type: none"><li>• IARC evaluation of TCDD determined that there was sufficient evidence of carcinogenicity in experimental animals (Baan et al. 2009)</li><li>• TCDD binding and activation of aryl hydrocarbon (AhR) receptor (Sorg 2014; Mimura and Fujii-Kuriyama 2003)</li><li>• TCDD altered expression of numerous genes including <i>CTP1A1</i> (Whitlock 1999)</li></ul> | <ul style="list-style-type: none"><li>• Elevated kidney cancer mortality among chlorophenoxy herbicide or chlorophenol production workers or sprayers exposed to TCDD or higher dioxins (Kogevinas et al. 1997)</li><li>• Excess kidney cancer mortality in a meta-analysis of TCDD-exposed individuals (Xu et al. 2016)</li></ul>                                  | <ul style="list-style-type: none"><li>• Highest tertile of IWLDs vs. never users, no lag: RR<sub>T3</sub> = 2.92 (95% CI: 1.65, 5.17; <i>p</i><sub>trend</sub> = 0.001)</li><li>• Similar associations in 10- and 20-y lagged analyses</li></ul>                              |
| Atrazine             | <ul style="list-style-type: none"><li>• Endocrine disruption and activation of the hypothalamic–pituitary–adrenal axis (Kucka et al. 2012; Fraites et al. 2009)</li><li>• DNA damage and oxidative stress (Liu et al. 2014; Jestadi et al. 2014; Abarikwu 2014; Pino et al. 1988)</li><li>• Kidney damage and dysfunction in rats (Santa Mariá et al. 1986)</li></ul>                                  | <ul style="list-style-type: none"><li>• Positive exposure–response association with ESRD among pesticide applicators in the AHS (Lebov et al. 2016)</li><li>• No association with kidney cancer in prior investigations of atrazine use and cancer risk among AHS pesticide applicators (Rusiecki et al. 2004; Beane Freeman et al. 2011)</li></ul>                 | <ul style="list-style-type: none"><li>• Two highest quartiles of IWLDs vs. never users, 20-y lag: RR<sub>Q3</sub> = 1.50 (95% CI: 1.05, 2.14); RR<sub>Q4</sub> = 1.43 (95% CI: 1.00, 2.03; <i>p</i><sub>trend</sub> = 0.02)</li></ul>   |
| Cyanazine            | <ul style="list-style-type: none"><li>• Limited evidence of mutagenicity and DNA damage (reviewed by Lynch et al. 2006)</li></ul>  | <ul style="list-style-type: none"><li>• No association with ESRD among pesticide applicators in the AHS (Lebov et al. 2016)</li><li>• Kidney cancer not evaluated in a prior investigation of cyanazine use and cancer risk among AHS pesticide applicators (Lynch et al. 2006)</li></ul>   | <ul style="list-style-type: none"><li>• Two highest quartiles of IWLDs vs. never users, 20-y lag: RR<sub>Q3</sub> = 1.86 (95% CI: 1.19, 2.90); RR<sub>Q4</sub> = 1.61 (95% CI: 1.03, 2.50; <i>p</i><sub>trend</sub> = 0.02)</li><li>• Similar results with 10-y lag</li></ul> |
| Paraquat             | <ul style="list-style-type: none"><li>• Evidence of nephrotoxic effects in animal models (summarized in Vaziri et al. 1979)</li><li>• Glomerular lesions and renal tubular necrosis resulting from oxidative stress-induced cellular damage (Adachi et al. 2000)</li></ul>   | <ul style="list-style-type: none"><li>• Acute kidney injury and kidney failure related to paraquat intoxication (Vaziri et al. 1979)</li><li>• Positive exposure–response association with ESRD among pesticide applicators in the AHS (Lebov et al. 2016)</li><li>• Husbands' use of paraquat associated with ESRD among AHS spouses (Lebov et al. 2015)</li></ul> | <ul style="list-style-type: none"><li>• &gt;Median IWLDs vs. never users, 20-y lag: RR<sub>M2</sub> = 1.95 (95% CI: 1.03, 3.70; <i>p</i><sub>trend</sub> = 0.04)</li></ul>  |
| Chlordane            | <ul style="list-style-type: none"><li>• IARC evaluation of chlordane determined that there was sufficient evidence of carcinogenicity in experimental animals (IARC 2001)</li></ul>  | <ul style="list-style-type: none"><li>• Positive exposure–response association with ESRD in 5-y lagged analysis among pesticide applicators in the AHS (Lebov et al. 2016)</li></ul>  | <ul style="list-style-type: none"><li>• Highest tertile of IWLDs vs. never users, 20-y lag: RR<sub>T3</sub> = 2.06 (95% CI: 1.10, 3.87; <i>p</i><sub>trend</sub> = 0.02)</li></ul>  |
| Chlorpyrifos         | <ul style="list-style-type: none"><li>• Oral administration induced histopathologic changes in the kidneys of male Wistar rats (Tripathi and Srivastav 2010)</li></ul>   | <ul style="list-style-type: none"><li>• No associations with RCC or ESRD observed previously among pesticide applicators in the AHS (Lee et al. 2004; Lebov et al. 2016)</li></ul>  | <ul style="list-style-type: none"><li>• Highest quartile of IWLDs vs. never users, 20-y lag: RR<sub>Q4</sub> = 1.68 (95% CI: 1.05, 2.70; <i>p</i><sub>trend</sub> = 0.01)</li><li>• Similar results with 10-y lag</li></ul>   |

Note: ESRD, end-stage renal disease; IARC, International Agency for Research on Cancer; IWLDs, weighted lifetime days of pesticide use; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

<sup>a</sup>Given the historical contamination of 2,4,5-T with TCDD during the manufacturing process, information on TCDD is included in this summary.

is believed to play a role (Xu et al. 2016; Sorg 2014; Mimura and Fujii-Kuriyama 2003). In the presence of TCDD, AhR induces or suppresses the transcription of numerous genes related to carcinogenesis, including *CYP1A1* (cytochrome P450 family 1 subfamily A member 1) (Whitlock 1999). With respect to RCC, in a study of 120 patients, Ishida et al. (2015) concluded that AhR regulates the invasion of clear cell RCC and may be involved in tumor immunity.

The potential health effects of 2,4,5-T, and its contaminant, TCDD, are of concern due to its widespread use during the Vietnam War. Agent Orange, a 50:50 mix of 2,4,5-T and 2,4-dichlorophenoxyacetic acid (2,4-D), was one of the most widely used defoliants during the Vietnam War, where approximately 65% of all herbicides contained this chemical (Stellman et al. 2003). Although many studies have examined the health effects of Agent Orange, most associations have been inconclusive (National Academies of Sciences, Engineering, and Medicine 2018). A recent large-scale evaluation of Agent Orange and cancer incidence and mortality among Korean veterans found significant excesses of all-site cancer incidence and mortality, but null findings for RCC incidence and mortality (Yi and Ohrr 2014; Yi et al. 2014). Similarly, a review of Agent Orange and

genitourinary cancers that included eight studies of renal cancer found that there was insufficient evidence to determine whether Agent Orange was associated with RCC (Chang et al. 2017), with small numbers of exposed cases in most studies and only one of the eight studies finding a statistically significant association (Kogan and Clapp 1988).

Atrazine and cyanazine, two broad-spectrum triazine herbicides used primarily on corn for weed control, were associated with increased risks of RCC in lagged exposure analyses. Atrazine was introduced in the late 1950s and has remained one of the most commonly used herbicides in the United States (U.S. EPA 2006) although it has been banned in Europe since 2004 (European Commission 2004). In contrast, cyanazine was developed in the early 1970s and banned in the United States in 2002 (U.S. EPA 1996). With respect to carcinogenicity, atrazine is currently not classified because of insufficient evidence (IARC 2015), whereas cyanazine is classified as a possible carcinogen based on increased mammary tumors in rats and mutagenic effects on lymphoma cells in mice (Lynch et al. 2006; U.S. EPA. 2018). Findings from experimental studies suggest that atrazine may induce DNA damage and oxidative stress (Liu et al. 2014; Jestadi et al. 2014; Abarikwu 2014; Pino et al. 1988) as well as

kidney damage and dysfunction in rats (Santa Mariá et al. 1986). However, for cyanazine there is only limited experimental evidence of mutagenicity and DNA damage (reviewed by Lynch et al. 2006). In terms of epidemiologic evidence, two recent reviews found no evidence of increased cancer risk for the triazine herbicide class or atrazine, specifically (Sathiakumar et al. 2011; Boffetta et al. 2013). With respect to prior AHS findings, two previous analyses of cancer risk in atrazine applicators found no association with kidney cancer (Rusiecki et al. 2004; Beane Freeman et al. 2011) although these investigations were conducted with a shorter follow-up period and included fewer exposed cases than this analysis.

We noted some evidence of association between paraquat and RCC, particularly in the 20-y lagged analyses. Paraquat is a widely used nonselective bipyridyl herbicide that is highly acutely toxic when ingested or inhaled. It is a restricted-use pesticide and classified as a Class 2, moderately toxic chemical (WHO 2010). Paraquat intoxication is characterized by acute kidney injury and other health effects, including potential multiple organ failure. After ingestion, paraquat is quickly absorbed in the renal cells, leading to severe oxidative stress, reduced kidney function, and renal cell damage (Møllck and Friis 1998; Mohamed et al. 2015). Despite its high toxicity, the potential carcinogenic effects of paraquat are less understood. The U.S. EPA has classified paraquat as a possible human carcinogen, mostly based on limited evidence of squamous cell carcinoma in exposed animals (U.S. EPA 2009). In a previous investigation of ever-use of paraquat and cancer incidence in the AHS, there was no evidence of an association with kidney cancer (20 exposed cases), with too few cases to evaluate lifetime days of use (Park et al. 2009). In contrast to a previous AHS analysis of trifluralin, where users in the highest exposure category had a nonstatistically significant 1.77-fold (95% CI: 0.73, 4.3;  $p_{\text{trend}} = 0.27$ ) risk of kidney cancer compared with nonusers (Kang et al. 2008), we found no evidence of increased RCC risk among users of this herbicide.

We also observed associations with two insecticides. Chlorpyrifos, an organophosphate insecticide, was associated with RCC in 10- and 20-y lagged exposure analyses. Chlorpyrifos was developed in the 1960s and became one of the most commonly used insecticides in the United States in the 1980s and 1990s (U.S. EPA 2017). To date, there has been no carcinogenic classification for chlorpyrifos by either the U.S. EPA or the IARC, and it is currently scheduled for registration re-review in 2022 (U.S. EPA 2017). With respect to renal damage, one experimental study observed histopathologic changes in the kidneys of male Wistar rats following oral administration of chlorpyrifos (Tripathi and Srivastav 2010). In a previous AHS analysis of cancer risk among applicators who used chlorpyrifos ( $n = 20$  exposed cases), the RR for kidney cancer in relation to ever use of chlorpyrifos was 1.08 (95% CI: 0.56, 2.06) (Lee et al. 2004). Another organophosphate, diazinon, showed a nonstatistically significant elevated risk of kidney cancer in a previous AHS analysis [RR<sub>lifetime days</sub> = 1.77 (95% CI: 0.90, 3.51;  $p_{\text{trend}} = 0.09$ ); RR<sub>intensity-weighted lifetime days</sub> 1.37 (95% CI: 0.64, 2.92;  $p_{\text{trend}} = 0.50$ )] (Jones et al. 2015). Similarly, in our 20-y lagged analysis, participants with intensity-weighted use of diazinon use above the median had a 1.36 higher relative risk of RCC compared with nonusers although the test of trend was not statistically significant (95% CI: 0.72, 2.58;  $p_{\text{trend}} = 0.34$ ).

Of the six organochlorine insecticides we evaluated, only chlordane was statistically significantly associated with an increased risk of RCC when exposure was lagged by 20 y. Chlordane was sold in the United States between the 1940s and 1980s, and most recently used for termite control. Like all organochlorines, chlordane belongs to the group of chlorinated hydrocarbon derivatives known for their toxicity, slow degradation, and bioaccumulation in

lipophilic tissue. Chlordane is classified as possibly carcinogenic by the IARC, based mainly on evidence from animal studies (IARC 2001), but it also has been linked with increased risks of several cancers in population-based studies, including non-Hodgkin lymphoma (Colt et al. 2006; Spinelli et al. 2007), rectal cancer (Purdue et al. 2007), liver cancer (Engel et al. 2019), and testicular cancer (McGlynn et al. 2008; Purdue et al. 2009).

Notably, for several of the pesticides associated with RCC in this investigation, similar patterns of association have been observed previously in the AHS for nonmalignant kidney disease. In an investigation of end-stage renal disease among pesticide applicators in the AHS (Lebov et al. 2016), statistically significant exposure–response associations were seen for intensity-weighted lifetime days of atrazine, paraquat, chlordane, and pendimethalin, which were also associated with RCC in lagged analyses in the present study. As summarized in Table 3, experimental evidence suggests that some of these chemicals may cause oxidative stress-induced cell damage leading to glomerular lesions, renal tubular necrosis, or kidney dysfunction (Santa Mariá et al. 1986; Adachi et al. 2000), which may contribute to renal carcinogenesis. Evidence from epidemiologic studies has demonstrated that impaired renal function is associated with an increased risk of RCC (Lowrance et al. 2014; Chow et al. 2018) and that certain demographic and personal characteristics are risk factors for both RCC and end-stage renal disease (Chow et al. 2018; CDC 2007), suggesting a shared etiology of malignant and nonmalignant kidney diseases. As such, this consistency with previously observed associations for end-stage renal disease supports the plausibility of our findings for RCC and suggests that exposure to some pesticides may influence risk of both outcomes.

The present prospective study is the largest and most comprehensive investigation of pesticide use and RCC risk to date. Participants were followed for incident RCC diagnoses for an average of 19.5 y, and we were able to evaluate exposure–response associations with up to 20 y of lagged exposure. Self-reported information on lifetime use of individual pesticides was determined to be of high quality and validity (Blair et al. 2002; Thomas et al. 2010). Nonetheless, we cannot rule out the possibility of some misclassification of exposure. Due to the prospective study design of the AHS, any exposure misclassification is likely to be nondifferential, resulting in attenuated risk estimates toward the null for binary exposure variables, although the directionality of bias is uncertain for polytomous categories (Blair et al. 2011; Rothman et al. 2008). We used a multiple imputation procedure to impute pesticide use for the participants who did not complete the follow-up questionnaire. Even though this imputation procedure is not specific for RCC, we previously showed that there was no evidence of bias in risk estimates when outcome was not considered (Andreotti et al. 2019). In addition, we cannot rule out the possibility of chance findings, particularly due to multiple testing. Given that this is this one of the first large-scale evaluations of pesticides and RCC, our findings are mostly exploratory and confirmation of the observed associations in other occupationally exposed populations and in continued follow-up of the AHS is needed.

In conclusion, in this analysis of RCC in a cohort of farmers and pesticide applicators, risk was most apparent and consistent for the herbicide 2,4,5-T in analyses with unlagged and lagged exposures for both lifetime days and intensity-weighted lifetime days of use. These findings, taken together with the mechanistic and experimental evidence and prior epidemiologic findings of excess kidney cancer mortality among chlorophenoxy herbicide or chlorophenol production workers or sprayers exposed to TCDD or higher chlorinated dioxins (Table 3), provide compelling evidence that exposure to 2,4,5-T and its contaminant TCDD may contribute to the development of RCC. Although 2,4,5-T is

no longer in use, this finding, if confirmed in other studies, has potential implications for Vietnam War veterans and civilians, including nearly 3 million U.S. service members, who may have been exposed to this herbicide and its contaminant TCDD resulting from widespread use of Agent Orange. In lagged analyses, we also found associations for three other herbicides—atrazine, cyanazine, and paraquat—and two insecticides—chlorpyrifos and chlordane. In addition to 2,4,5-T, there is also plausible mechanistic and experimental data for atrazine and paraquat in relation to kidney damage and dysfunction as well as positive epidemiologic associations with renal disease (Table 3). Nevertheless, given that this is one of the first prospective studies able to assess the risk of RCC in relation to various specific pesticides, the findings require replication. Experimental and molecular epidemiologic studies, including possible mediating effects of renal disease, are needed to help establish the biological plausibility and potential mechanisms of action underlying the observed associations with RCC.

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